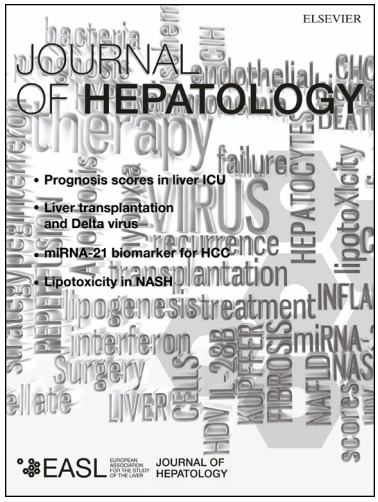

Letter to the Editor

The beginning of an endpoint: peak AST in liver transplantation

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PII: S0168-8278(14)00520-0
DOI: http://dx.doi.org/10.1016/j.jhep.2014.07.021
Reference: JHEPAT 5262

To appear in: *Journal of Hepatology*

Received Date: 1 July 2014
Accepted Date: 7 July 2014

Please cite this article as: Jochmans, I., Monbaliu, D., Pirenne, J., The beginning of an endpoint: peak AST in liver transplantation, *Journal of Hepatology* (2014), doi: http://dx.doi.org/10.1016/j.jhep.2014.07.021

The beginning of an endpoint: peak AST in liver transplantation

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Word count: 796

Number of figures: 1

List of abbreviations: EAD, early allograft dysfunction; AST, aspartate transaminase; POD, postoperative day

Conflict of interest: none

Financial support: none

To the Editor

In their review on liver graft quality assessment during preservation, Verhoeven et al. [1] point out a painful weakness that continues to hamper progress in the field of liver transplantation. The lack of validated markers that reliably predict graft quality and function make comparison of trial results and meta-analysis impossible. There is an urgent need for international guidelines on appropriate endpoints to assess liver graft quality and function and the authors refer to early allograft dysfunction (EAD) as described by Olthoff et al. [2] as a starting point. Indeed, EAD and particularly peak aspartate transaminase (AST), one of the EAD components, are increasingly used as primary endpoint in liver transplantation trials aimed to improve (early) graft function (e.g. ISRCTN00167887; ISRCTN39731134). When determining the peak of a marker, it is essential that kinetics of this marker and especially the timing of the peak be precisely known so that determination of that peak can be as accurate as possible. Although AST is a well-recognized marker for hepatocyte injury and used as a surrogate to assess preservation and ischemia-reperfusion injury, it is remarkable how little information is available on the kinetics of AST post-reperfusion. It is generally assumed that AST peaks within the first 24 to 72h post-reperfusion [3, 4]. However, considering AST is released quickly from injured hepatocytes and is also quite rapidly cleared, it is not unthinkable that a peak – particularly an early one – might be missed if samples are not precisely taken. We therefore determined the evolution of AST early post-reperfusion, and the timing of its peak. In addition, we compared the peak AST and its timing in timed post-reperfusion samples versus routinely taken samples that are usually used to determine peak AST in clinical trials.

We analyzed post-reperfusion AST values in 66 adult liver-only recipients [60 years (48-67), 38 males] transplanted between 11/2011 and 11/2013 who had consented for a prospective observational study on kidney injury during liver transplantation (NCT01333319, approved by Ethical Committee). In this study, plasma samples were taken at time of incision, 30 min, 2h, 6h, and 12h post-reperfusion. Furthermore, recipients had routine AST determinations with a first AST sample "at arrival on the intensive care unit" and daily morning measures until postoperative day (POD) 5. The post-reperfusion timing of these routinely taken samples was retrospectively determined from the electronic patient records. AST was determined in the hospital's central lab (coloric method, Hitachi/Roche Modular P). Continuous variables [median (inter quartile range)] were compared between timed and routine samples by the Mann-Whitney U test (SPSS version 19).

Donors were 57 (44-68) years old and livers were transplanted with a cold ischemia time of 6h (5-8) and anastomotic times of 45 min (40-45). Indications for liver transplantation were acute liver failure (n=7), HCV/HBV cirrhosis (n=12), cholestatic cirrhosis (n=13), post-ethyl cirrhosis (n=14), NASH cirrhosis (n=5), cryptogenic cirrhosis (n=4), retransplantation (n=4) and others (n=7). In 28 cases a simultaneous hepatocellular carcinoma was present, accounting for the fact the MELD at time of transplantation was low [13 (10-18)]. Indeed, Eurotransplant awards "exceptional" MELD points in case of hepatocellular carcinoma within Milan criteria [5]. Eleven livers were donated after circulatory death with a total warm ischemia time in the donor of 23 min (16-27).

The AST kinetics show that AST increases immediately after reperfusion to peak at 6h, after which there is a steady decrease with values halved by POD1 (Fig.1A). Both the peak and the timing of the AST peak were similar between timed and routinely taken blood samples in this

study population [6h (6-6) vs. 6h (5-11), p=071; 948 IU/L (593-1508) vs. 908 IU/L (512-1146), p=0.46; respectively] with 90% of AST peaks detected in the first 14h (Fig.1B and C).

In clinical trials with peak AST as primary endpoint the time window set to determine that AST peak is often wide (up to POD7). Furthermore the timing of the first AST measurement is rarely predefined and mostly relies on routinely taken samples. In this liver transplant cohort the majority of peak ASTs are detected at 6h post-reperfusion with a time window between 5h and 11h, considerably earlier that what is usually assumed. Therefore, relying on routine blood samples to correctly measure the AST peak should only be done if the first routine sample is taken in this time period. Subsequently, clinical trials using peak AST as primary endpoint should clearly define the timing of the first blood sample and specify a time window for this sample in the trial protocol. Based on the cohort presented here, this could appropriately be defined as a sample taken anywhere between 5h and 11h after reperfusion and in our experience will often be the first blood sample taken in the intensive care unit.

Acknowledgement

We thank Ilse Senesael and all medical students that helped with sample collections.

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Figure Legends

Fig.1. AST kinetics and timing of peak values after reperfusion

Panel (A) shows the post-reperfusion kinetics of AST (mean ± SD) in 66 liver transplant recipients early after reperfusion (from 30 min until 12h) and daily until postoperative day 5. Peak AST values measured in routinely taken or timed blood samples are not different in this population (p=0.71) (Panel (B)). The timing of the AST peak is shown in panel (C) and is also similar between routinely taken and timed blood samples (p=0.46).